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Short Communication

Feline Atopic Dermatitis

A Model for Langerhans Cell Participation in Disease Pathogenesis

Petra J. Roosje,*† Diana Whitaker-Menezes,‡ Michael H. Goldschmidt,§ Peter F. Moore,‖ Ton Willemse,† and George F. Murphy‡

From the Departments of Clinical Studies and Veterinary Pathology,§ School of Veterinary Medicine, the Department of Dermatology,‡ School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, the Department of Pathology, Microbiology, and Immunology,‖ University of California, School of Veterinary Medicine, Davis, California, and the Department of Clinical Sciences of Companion Animals,† Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands*

Atopic dermatitis is a disorder characterized by cutaneous exanthemata as a consequence of exaggerated eczematous reactions to topical and systemic allergens. Langerhans cells, expressing CD1a and HLA-DR, and dermal dendritic cells, expressing HLA-DR, are known to be potent antigen-presenting cells and are thought to play an important role in the pathogenesis of atopic dermatitis. The immunophenotype of lesional skin in atopic dermatitis in humans involves increased numbers of CD1a$^+$/MHC class II$^+$ dendritic cells in addition to activated T cells, mast cells, and macrophages. To establish feline skin as a model for the study of human atopic dermatitis, and to elucidate the role of dendritic cells in feline atopic dermatitis, we investigated the presence of CD1a$^+$ cells and MHC class II$^+$ cells in the epidermis and dermis of lesional feline skin and in skin of healthy control animals. Immunohistochemistry revealed that MHC class II$^+$ epidermal dendritic cells were CD1a$^+$ in normal feline skin and significantly increased numbers of CD1a$^+$ cells and MHC class II$^+$ cells were present in the epidermis and dermis of lesional skin. These data provide the first correlative documentation of CD1a expression by feline dendritic cells containing Birbeck granules, and indicate the utility of feline skin in the study of human cutaneous atopy. ***(Am J Pathol 1997, 151:927–932)***

Langerhans cells (LCs) and dermal dendritic cells (DDCs) are known to be potent antigen-capturing and -presenting cells and are thought to play an important role in the pathogenesis of atopic dermatitis (AD) in humans.[1,2] Langerhans cells at the site of patch tests to aero-allergens in patients with AD show increased activity.[3] In lesional skin of AD patients, increased numbers of CD1$^+$ and HLA-DR$^+$ cells have been found in the dermis and to a lesser extent in the epidermis.[2] In addition, LCs from AD patients depend on surface IgE to mount specific T cell responses to house dust allergen (HDA), both *in vivo* and *in vitro*.[4] After capture, the internalized antigen is processed and presented to T cells in a MHC class II restricted way.[5] T cells and their cytokines are the next step in the complex network that contributes to allergic inflammation.[6,7]

In contrast to humans, little is known about the pathogenesis of AD in feline species. Various observations indicate similarity to the human disease. In cats, the histopathology of AD is characterized by perivascular and diffuse dermal infiltrates of lymphocytes, mast cells, eosinophils, and macrophages,[8] findings comparable to the infiltrates seen in humans with AD.[9] Recently, we described an increased number of CD4$^+$ T cells and interleukin (IL)-4 expression by these cells in lesional skin of AD cats, supporting a role for T_{H2}-dependent pathways in disease pathogenesis.[10] Additionally, a putative feline IgE has been described in cats,[11,12] and reports exist that show familial involvement in feline AD.[13] Although cats have been used with success as an exper-

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P. J. Roosje's present address: Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht, The Netherlands.

D. Whitaker-Menezes' and G. F. Murphy's present address: Jefferson Medical College, Department of Pathology, Anatomy, and Cell Biology, Philadelphia, PA.

Address reprint requests to Dr. Ton Willemse, Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, PO Box 80.154, 3508 TD Utrecht, The Netherlands.

imental model of airway hyperresponsiveness,[14,15] to our knowledge no studies exist on the use of cats as an experimental model for AD in man.

The aim of this study was to explore the suitability of feline skin to serve as a model for participation of Langerhans cells in AD. Specifically, first we determined the presence of $CD1a^+$ cells in lesional skin of allergic cats, and second we assessed the relationship of MHC class II expression to CD1a. The data indicate that feline skin harbors $CD1a^+$ Langerhans cells analogous to those in human skin, and suggest active participation of these cells in feline AD.

Materials and Methods

Animals

Skin biopsies were obtained from nine domestic shorthair cats with a history of recurrent allergic dermatitis. The age of these cats was 3 to 11 years (median, 7 years; five spayed female cats and four castrated male cats). These cats were selected according to the clinical criteria for feline AD,[8] the presence of immediate skin test reactivity, and compatible histopathology of skin biopsies. Food hypersensitivity, dermatophytosis, and ectoparasites were excluded.[8]

Three 6-mm punch biopsies were taken from lesional skin of AD cats (n=9). Two biopsies were used for routine hematoxylin and eosin (H&E) staining to confirm the histopathological features of allergic dermatitis and one biopsy was immediately snap-frozen in liquid nitrogen.

Skin biopsies from the healthy control animals (n=9) were obtained from the same body location and processed in the same manner. The age of these cats was 3 to 12 years (median, 6.6 years; four spayed female cats and five castrated male cats). Before taking skin biopsies all cats were anesthetized with ketamine, xylazine, and atropine.

Immunohistochemistry

Single staining was performed with a mouse monoclonal antibody (MAb) to feline CD1a (FE1.5F4) and a mouse MAb against feline MHC class II (42.3).[16] From each biopsy 6-μm sections were cut using a cryostat (Reichert Histostat). Sections were air dried and stored at −80°C until used. Before staining, serial sections were fixed with acetone and 0.3% hydrogen peroxide to quench endogenous peroxidase. Nonspecific binding was blocked by preincubation for 20 minutes with 100% horse serum. The antibodies to CD1a and MHC class II were applied in different dilutions, and sections were incubated overnight at 4°C. Biotin-conjugated horse anti-mouse antibody was used as a second step followed by incubation with an avidin-biotin-horseradish peroxidase complex (Vector ABC Elite kit, Vector Laboratories, Burlingame, CA).[17] Reactive sites were revealed using 3,3′-diaminobenzidine (Sigma Chemical Co., St. Louis, MO) as the chromogen. Control procedures included substitution of primary MAb with irrelevant isotype-specific mouse MAbs. Sections were lightly counterstained with diluted Gill's hematoxylin solution.

Double-immunofluorescence staining with CD1a, MHC class II, and MAb anti-feline CD4 (vpg 34)[18] at different dilutions was also performed. Sections were fixed with acetone, and the mouse anti-feline CD1a was applied for 1 hour at room temperature. A polyclonal rabbit anti-mouse (Dako, Carpinteria, CA) was used as a secondary antibody, followed by a fluorescein-conjugated donkey anti-rabbit antibody (Accurate Scientific, Westbury, NY). After washing, the mouse anti-feline MHC class II antibody was administered and left for 1 hour at room temperature. A Texas-Red-conjugated sheep anti-mouse antibody (Accurate Scientific) was used as a second step. Negative controls consisted of irrelevant isotype-matched antibodies. Sections were evaluated with an Olympus BX 60 fluorescence microscope equipped with the appropriate excitation and emission filters for fluorescein and Texas Red illumination.

Ultrastructural Analysis

Skin biopsies of three allergic and three healthy control animals were processed for electron microscopy. Briefly, tissue was placed in Karnovsky's fixative at 4°C and stored until further processing.[19] Samples were then post-fixed with 2% osmium tetroxide for 1.5 hours, dehydrated through graded ethanols followed by propylene oxide, and embedded in Taab Epon 812 (Marivac, Nova Scotia, Canada). Ultrathin sections were cut on an LKB Ultratome III ultramicrotome, post-stained with uranyl acetate and bismuth subnitrate and viewed on an Hitachi H-7000 electron microscope.

Statistical Analysis and Cell Quantification

Positive staining cells in the epidermis and underlying dermis were counted separately with a square reticule in five adjacent high-power fields (×400). Results were expressed in cells/linear mm in the epidermis or in cells/mm^2 in the dermis. Only highly dendritic cells with a clearly visible cell body were counted. Positive staining cells in hair follicle walls were not included. To compare feline AD skin with normal skin for CD1a and MHC class II expression, a Mann-Whitney test was performed for comparison of cell number within the epidermis and within the dermis of both animal groups. The Spearman Rank correlation test was used to test for correlation between the epidermal and dermal parameters.

Results

H&E staining of the skin of the healthy control cats revealed no abnormalities. By immunohistochemistry, the normal feline skin was found to contain $CD1a^+$ dendritic cells primarily within the epidermis: median, (10 cells/linear mm; range, 4 to 25; Figure 1A); 75% (range, 0 to 100%) of these cells showed immunohistochemical co-expression of MHC class II (Figure 1B), further defining

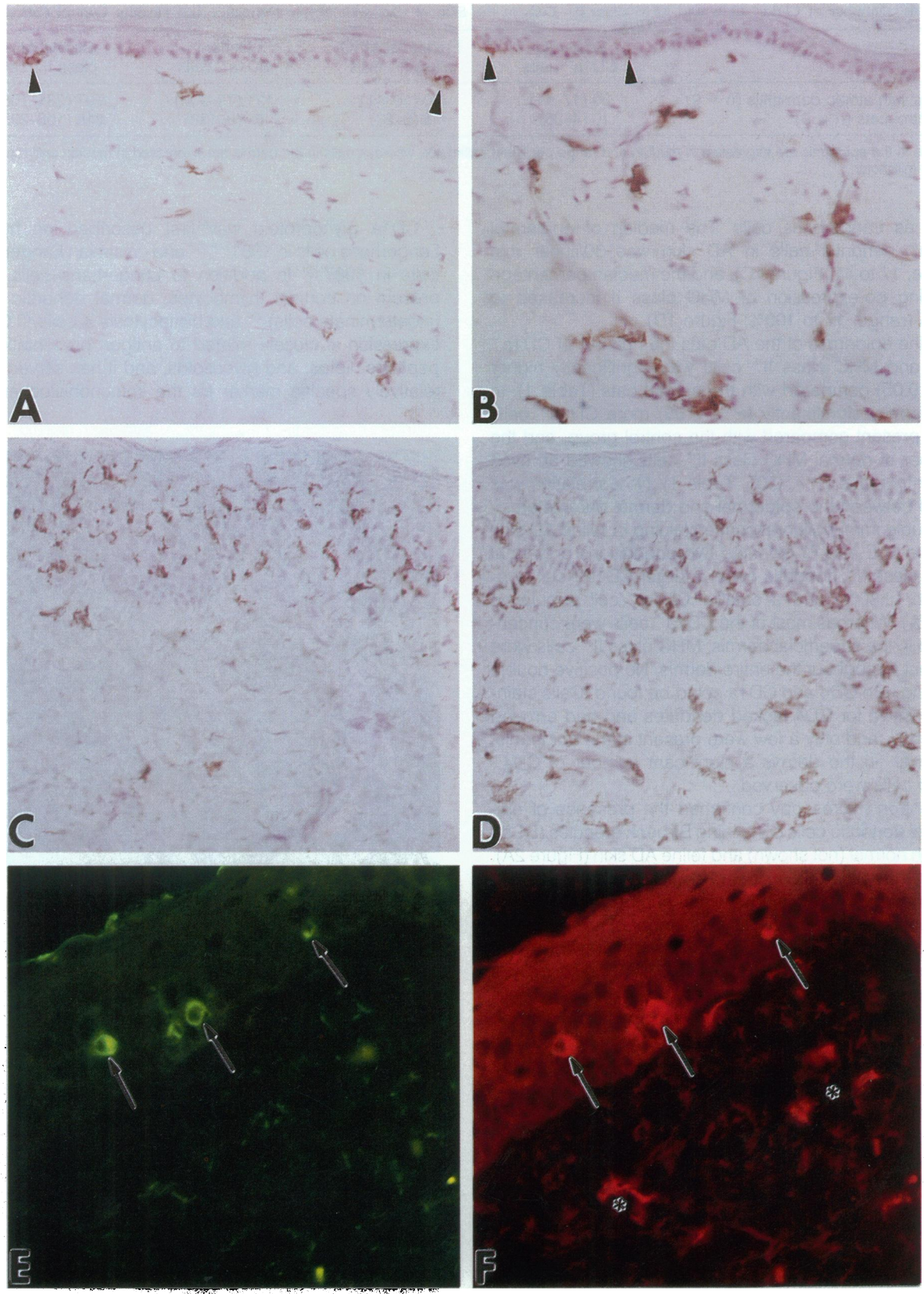

Figure 1. Immunohistochemical and immunofluorescence evaluation of normal and atopic feline skin. **A**, **C**, and **E**: $CD1a^+$ cells. **B**, **D**, and **F**: MHC class II^+ cells. In normal skin (**A** and **B**), occasional $CD1a^+$ (**A**) and MHC class II^+ (**B**) cells are observed within the thin epidermal layer (**arrowheads**) and in the underlying dermis (endothelial cells also show variable MHC class II reactivity). In atopic skin (**C** and **D**), there is a marked increase in number of highly dendritic $CD1a^+$ (**C**) and MHC class II^+ (**D**) cells within the thickened epidermal layer. By double labeling of sections of atopic dermatitis skin (**E** and **F**), the majority of $CD1a^+$ cells (**E**, **arrows**) are also MHC class II^+ (**F**). Note the presence of MHC class II^+ $CD1a^-$ cells (**asterisk** in **F**) within the dermis. Magnification, ×400.

Table 1. Number of $CD1a^+$ Cells and MHC Class II^+ Cells in the Skin of Cats with Atopic Dermatitis and Healthy Control Cats

	Epidermal $CD1a^+$ cells	Epidermal MHC class II^+ cells	Dermal $CD1a^+$ cells	Dermal MHC class II^+ cells
Cats with atopic dermatitis (n = 9)	30 (17–41)	30 (10–41)	121 (72–200)	707 (231–1081)
Control cats (n = 9)	10 (4–25)	8 (0–26)	61 (8–136)	216 (106–295)

Cells in the epidermis are expressed in median and range per linear millimeter, whereas cells in the dermis are expressed in median and range per square millimeter.

them as Langerhans cells. The median of epidermal $CD1a^+$ dendritic cells in AD skin was 30/linear mm (range, 17 to 41; Figure 1C), and the median percentage showing co-expression of MHC class II increased to 100% (range, 17 to 100%; Figure 1D).

In the epidermis of the AD cats the number of $CD1a^+$ cells and MHC class II^+ cells was significantly higher ($P < 0.05$) compared with the normal cats (Table 1). In the dermis, significantly ($P < 0.05$) more $CD1a^+$ cells were present compared with the control group, and the number of dermal MHC class II^+ cells showed an even larger increase ($P < 0.05$; Table 1). No correlation was found between the epidermal and dermal parameters.

Double immunofluorescence staining of feline AD skin (Figure 1, E and F) revealed two populations of dermal MHC class II^+ dendritic cells: a larger $CD1a^-$ cell population (±80%) and a smaller $CD1a^+$ cell population (±20%). Whereas most of the $CD1a^+$ cells were concentrated in the superficial dermis, MHC class II^+ cells were present throughout the entire dermis. No positive double staining with CD4 and CD1a could be found. Cells staining positive for CD4 lacked dendrites and had a round cell body, and only a few were present in the epidermis. However, in the dermis a significant number of $CD4^+$ round cells were observed.

Electron microscopy confirmed the presence of epidermal dendritic cells containing Birbeck granules (BGs), in both normal (not shown) and feline AD skin (Figure 2A). Within the epidermis of control skin only a few epidermal dendritic cells containing a small number of BGs were demonstrated, whereas a larger number of tennis-racket-shaped BGs and zipper-like BGs were present in the epidermal dendritic cells of feline AD skin. Additionally, it appeared qualitatively that more BG-containing cells were present in the suprabasal and basal layers of feline AD epidermis, whereas in the normal epidermis, dendritic cells were primarily present in the basal layer with an occasional dendritic cell in the suprabasal layer. BG-containing cells had a more activated phenotype consisting of a prominent Golgi and many lysosomes (Figure 2B) as compared with normal skin. BG-containing cells could not be found in the normal dermis or in the feline AD dermis.

Discussion

In the present study we document for the first time correlative evidence for the presence of CD1a glycoprotein on feline epidermal dendritic cells, and we use this technique to study alterations in $CD1a^+$ and MHC class II^+ dendritic cells in cats with AD.

CD1a glycoprotein was first described on human Langerhans cells in 1981[20–22] and on simian Langerhans cells in 1987.[23] In addition to Langerhans cells, it is present on cortical thymocytes, dermal dendritic cells (indeterminate cells),[24] and histiocytosis X cells.[25] CD1a expression is closely related to antigen presentation of peptides, lipids, and glycolipids, and it has served as a relatively specific marker for the immunohistochemical

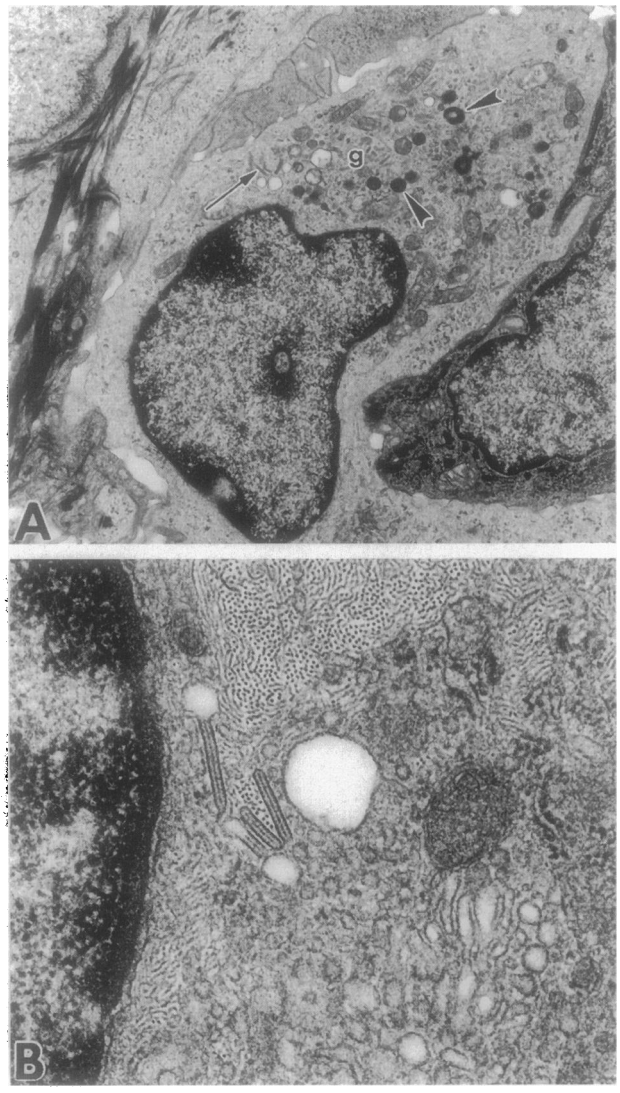

Figure 2. Transmission electron microscopy of intraepidermal Langerhans cell in atopic feline skin. **Arrow** in **A** indicates Birbeck granules (enlarged in **B**). Also note the prominent Golgi zone (g) and associated lysosomes (**arrowheads**) consistent with immunological activation. Magnification, ×8,400 (**A**) and ×43,500 (**B**).

detection of cells with this functional profile. Langerhans cells have been shown to express the high-affinity receptor for IgE (FcϵRI),[26,27] and serum-IgE-facilitated allergen presentation in atopic disease was demonstrated.[28] LCs also play a potentially important role in harboring a certain retrovirus implicated in immunodeficiency.[29] Recognition of CD1a expression by Langerhans cells of an animal species such as the cat, which is prone to development of IgE-mediated skin allergy as well as retrovirus-associated immunodeficiency, should enhance utilization of this model for investigation of these and related disorders.

Other indications for the suitability of feline AD as a model for human AD were described by the presence of an increased number of CD4$^+$, IL-4-producing T cells in lesional skin of AD cats[10] and a similar cellular infiltrate containing eosinophils, mast cells, lymphocytes, and macrophages. The presence of eosinophils in lesional skin may be explained by their recruitment elicited by cytokines such as IL-4, IL-5, and granulocyte/macrophage colony-stimulating factor produced by T_{H2} cells.[30]

In the atopy patch test in humans, eosinophils were shown to infiltrate into the dermis 2 to 6 hours after allergen application and were in an activated state after 24 to 48 hours, although, later, primarily eosinophil granular products were present.[31] Although in humans with chronic AD the number of mast cells is increased,[9] in acute lesions the mast cells are normal in number but in different stages of degranulation.[9] Their precise role in human AD is still obscure. In cats with AD the number of mast cells is increased, and with electron microscopy we noticed different stages of degranulation (data not shown).

In this study, the presence of CD1a$^+$ cells and MHC class II$^+$ cells in the epidermis and dermis of normal cats and of lesional skin of cats with feline AD were investigated to elucidate the role of antigen-presenting cells in this disease. In the AD cats, an increased number of CD1a$^+$ cells in the epidermis was detected compared with the control animals, a finding comparable to skin of humans with AD.[2]

The decreased expression by Langerhans cells of MHC class II compared with CD1a in the normal epidermis was similar to that described in humans where antibody to CD1a was found to label more Langerhans cells than HLA-DR.[32] A marked increase in MHC class II$^+$ dendritic cells was also seen in the epidermis of feline AD skin compared with control skin, which is consistent with the up-regulation of MHC class II after cytokine-mediated Langerhans cell activation.[33,34] We found only small numbers of intra-epidermal T cells in lesional feline skin in an earlier study,[10] and only dendritic cells were counted in this study; therefore, we excluded intra-epidermal T cells as MHC class II$^+$ cells.

The up-regulation of MHC class II is primarily induced by interferon (IFN)γ, which is predominantly produced by the T_{H1} subset, not the T_{H2} subset implicated in feline AD.[10] However, recently the presence of IFN-γ was demonstrated in lesional skin after atopy patch tests in patients with AD, confirming a shift from a T_{H2} response to a T_{H1} and T_{H0} response.[35,36]

Although all of the AD cats had a history of chronic recurrent AD, there were differences in duration of the disease. The wide range in CD1a$^+$ and/or MHC class II$^+$ cells may reflect a more or less active stage of the disease. Although one animal did not have MHC class II$^+$ cells in the epidermis, this could not be attributed to a staining error because MHC class II$^+$ cells were present in the underlying dermis. The marked increase of dermal MHC class II$^+$ cells was comparable to what is seen in humans.[2] Although Langerhans cells in humans express the CD4 marker,[37] we were not able to demonstrate its presence on the feline dendritic cells and we could not demonstrate up-regulation of CD4 upon activation. Possible explanations are that the MAbs used lacked sensitivity or that the CD4 levels on the Langerhans cells were too low for detection with the technique used.

Based on morphology, the main population expressing the MHC class II consisted of DDCs. Different subsets of this MHC class II$^+$ DDC population in humans have been described, each expressing a different combination of markers.[38] In cats, only factor XIIIa$^+$ DDCs were described, but no double staining for MHC class II or other markers was performed.[39] Therefore, additional studies are needed to investigate the existence of similar subsets in cats.

With electron microscopy we were able to identify BGs that had a similar configuration to BGs in humans. Although zipper-like structures were reported in a small proportion of CD18$^+$ feline dendritic cells in an epidermal cell suspension,[40] no tennis-racket-shaped BGs in feline Langerhans cells were described *in situ*. Small numbers of BG-containing cells have been described in DDCs in humans, defining them as LCs;[41] however, we could not find BG-containing cells in the dermis of normal or feline AD skin. The location of Langerhans cells in normal feline skin was different from the situation in humans where Langerhans cells are normally suprabasilar in location,[42] whereas in the cats they were primarily basilar in location.

In summary, it appears that 1) MHC class II$^+$ epidermal dendritic cells are CD1a$^+$ in normal feline skin and 2) increased numbers of MHC class II$^+$ and CD1a$^+$ cells are present in the epidermis and dermis of lesional skin. These data indicate that LCs, related DDCs, and other MHC class II$^+$ cells may actively participate in feline AD and aid in establishing feline AD as a relevant model for the immunopathogenesis of this common and poorly understood human disease.

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